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REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claim 64 has been revised so as to be placed in independent form. In claim 64, the predetermined metabolic signal comprises a change in pH.

Claims 65 and 66 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is believed to be in order in view of the fact that the Examiner's own comments make it clear that the language does not lack definiteness. Reconsideration is requested.

Claims 42, 45-49, 51, 52, 54, 55, 58, 61 and 64-66 stand rejected under 35 USC 103 as allegedly being obvious over Meers et al (USP 6,087,325) in view of Parente et al. The rejection is traversed.

Independent claim 42 relates to a highly sensitive method for detecting target cells in a sample. The method comprises treating the sample with lipid vesicle particles, targeted to a targeted cell type. The particles have at least one layer of enveloping lipids and incorporate a cytolytic peptide that is non-covalently attached thereto. In response to a metabolic signal from the target cells, the cytolytic peptide interacts with the layer to act as or mediate to the opening of pores or channels within the lipid layer. Permeability of the particles is thereby modulated. The particles also incorporate a species that is activated upon such modulation of permeability and the species is directly or indirectly monitored. Independent claim 64 requires that the metabolic signal comprise a change in pH.

The methods disclosed in Meers et al and Parente et al are intrinsically incompatible. Absent knowledge of the present invention, one skilled in the art would not have considered

combining their teachings. Certainly, nothing in the citations themselves would have motivated their combination.

Meers et al discloses the use of a non-cytolytic stabilizing peptide that is covalently attached to the hydrophilic lipid head groups of the lipid layer of the liposome for treating diseases. The peptide acts as a blocking group to stabilize intrinsically unstable liposomes. Upon peptidase cleavage of the peptide, the bilayer structure of the membrane destabilizes, thereby causing the unstable liposome to fall apart by virtue of disruption of the aqueous periphery as opposed to the hydrocarbon phase.

The lipid vesicle particles of the present invention, having at least one layer of enveloping lipids and incorporating a cytolytic peptide, which is non covalently attached, are clearly different from the liposomes disclosed of Meers et al. While the Examiner acknowledges that Meers et al does not teach the use of a cytolytic peptide, as required by the claims, the Examiner contends that it would have been obvious to combine Meers et al with Parente et al, which discloses use of the peptide, GALA (i.e. a cytolytic peptide). Applicants respectfully, but vigorously, disagree.

As pointed out above, Meers et al relates to a method of treating diseases. Parente et al, on the other hand, is a study of the effect of GALA on pre-formed liposomes with regard to leakage of vesicle contents. More particularly, the study involved production of vesicles having a "detectable content" (first two paragraphs of the "Materials and Methods" section on page 5720) and incubating these vesicles in the presence of GALA (right hand column on page 8721 at lines 13 and also at line 44). The effect of the GALA on inducing leakage of the vesicle contents was then investigated. Parente et al discloses the mechanism of leakage (page 827), which involves incorporation of the GALA in the lipid bilayer to produce a channel.

Importantly, however, Parente et al **does not** start with liposomes that incorporate GALA. Rather, Parente et al is a study of the mechanism by which GALA, added separately to liposomes, induces leakage of liposome content.

The Examiner's assertions to the contrary, no basis is seen for combining the liposomes of Meers et al, which destabilize upon cleavage of the non-cytolytic peptide blocking group covalently attached to the hydrophilic lipid head group of the lipid layer of the liposome, with the cytolytic peptide of Parente et al. Nothing in Meers et al would have suggested the use of a means of effecting permeabilization of the liposome, other than the one specifically taught by Meers et al. It is only with hindsight of the present invention that the Examiner could contend otherwise. Further, even if one had looked to Parente et al, one would not have found a suggestion of the present detection method which, unlike Parente et al, involves the use of lipid vesicle particles "having at least one layer of enveloping lipid and incorporating a cytolytic peptide". As pointed out above, in Parente et al, GALA is added separately to liposomes. In summary, nothing but hindsight would have resulted in the combination upon which the Examiner relies and, even if such a combination had been made, one would not have arrived at the present invention.

In view of the above, reconsideration is requested.

Claim 50 stands rejected under 35 USC 103 as allegedly being obvious over Meers et al (USP 6,339,069) in view of Parente et al and further in view of Li et al. It is believed that Meers et al (USP 6,087,325) was intended, however, the Examiner is requested to clarify the record in this regard. In any case, the rejection is traversed.

The fundamental failings of Meers et al, taken alone or in combination with Parente et al, are detailed above. Nothing in any teachings of Li et al regarding the use of binding agents would have cured those deficiencies. Accordingly, reconsideration is requested.

Claims 56-57 stand rejected under 35 USC 103 as allegedly being obvious over Meers et al in view of Parente et al and further in view of Levinson et al. The rejection is traversed.

The distinctions between the present invention and the combination of Meers et al and Parente et al are discussed above. The addition of Levinson et al's teachings relating to delivery would not have brought one skilled in the art any close to the present invention. Accordingly, reconsideration is requested.

Claim 59 stands rejected as obvious over Meers et al in view of Parente et al and Robinson et al. Claim 60 stands rejected as obvious over Meers et al in view of Parente et al and Blondin et al. These rejections are also traversed.

Any teaching in Robinson et al relating to the analysis of food stuffs and any teaching in Blondin et al relating to detection of toxins in water samples would not have cured the failings of Meers et al and Parente et al (discussed in detail above) and thus would not have rendered obvious the subject matter of claims 59 and 60, respectively. Reconsideration is requested.

CLARKE et al
Appl. No. 09/529,342
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This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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